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(Poly) Thiaalykynoic compounds and their derivatives, compositions comprising them and their use

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ABSTRACT OF THE DESCRIPTIVE CONTENT OF THE INVENTION

(Poly)thiaalkynoic compounds and their derivatives, compositions comprising them and their use

The invention relates to the compounds of general formula (I):

R_1-Y-CH2-C≡C-CH2-S-CH2-R2

as well as the use of the latter in pharmaceutical or cosmetic compositions.

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L'OREAL

Invention Title:

(POLY) THIAALKYNOIC COMPOUNDS AND THEIR DERIVATIVES, COMPOSITIONS COMPRISING THEM AND THEIR USE

The following statement is a full description of this invention, including the best method of performing it known to me/us:

1A

The invention relates to (poly)thiaalkynoic compounds as novel and useful industrial products. It also relates to the use of these novel compounds in pharmaceutical compositions intended for use in human or veterinary medicine, or alternatively in cosmetic compositions.

These compounds of general formula (I) in accordance with the invention exhibit activity with respect to the transactivation of receptors of the PPAR type and more particularly of receptors of the PPAR-α subtype and find applications in particular in the treatment of inflammatory conditions such as rheumatoid arthritis, lupus and psoriasis in particular.

It is also possible to use the compounds according to the invention in cosmetic compositions for body and hair hygiene in particular to regulate the metabolism of cutaneous lipids, to restore the skin barrier function or to promote differentiation and to inhibit epidermal proliferation.

It is known that a number of substances play an important role in the inflammatory process in the skin such as acne, dermatoses, such as for example psoriasis, eczema, and the like. These substances, among which are prostaglandins, hydroxyeicosatetraenoic acids, thromboxanes and leukotrienes, all have a common origin which is arachidonic acid (see in particular

"VOORHEES Leukotrienes and other Lipoxygenase Products in the Pathogenesis and Therapy of Psoriasis and Other Dermathoses" Arch. Dermatol., Vol. 119, July 1983, 541-547).

The formation of these substances results essentially from the conversion, after release, of the arachidonic acid bound by an ester bond to the lipids present in the epidermis (for example the phospholipids).

There have previously been recommended, for the treatment of skin diseases, either cyclooxygenase inhibitors which prevent the formation of prostaglandins such as indomethacin, vitamin E, and the like; or substances capable of inhibiting lipoxygenases such as eicosatetraynoic acid.

There have also been proposed, for the treatment of psoriasis, 5,8,11,14-eicosatetraynoic acid as well as 5,8,11-eicosatriynoic acid and their lower alkyl esters, especially in patent US-A-4,190,669 or alternatively the replacement of the methylene group at the 3-position in the structure of 5,8,11-eicosatriynoic acid or of 5,8,11,14-eicosatetraynoic acid with a heteroatom such as sulphur or with a sulphoxide or sulphone group, especially in patent EP 342 115.

The applicant has discovered, surprisingly, that by shortening the length of the chain of unsaturated fatty acids of the thiaeicosa(poly)ynoic type, products were obtained which are activators of PPAR-type receptors and more particularly activators which are selective for a subtype of PPAR-α receptors.

These acids have, in addition, the advantage of having a cost price which is a lot more advantageous than their longer-chain homologues.

The applicant has also discovered, surprisingly, that by replacing the methylene group at the 8-position in the unsaturated 3-thia fatty acid chain with a heteroatom such as sulphur or with a sulphoxide or sulphone group, activators of PPAR-type receptors and more particularly activators which are selective for a subtype of PPAR-α receptors were also obtained.

The subject of the invention is therefore these new acids as well as their derivatives such as the esters and amides.

The compounds according to the invention may be represented by the following general formula (I):

$$R_1\text{-}Y\text{-}CH_2\text{-}C{\equiv}C\text{-}CH_2\text{-}S\text{-}CH_2\text{-}R_2 \qquad (I)$$

in which:

-Y represents:

(a) an -S(O)t radical,

t is an integer equal to 0, 1 or 2,

(b) a $-CH_2-$ radical,

(c) a -C≡C- radical,

(d) a -C=C- radical,

- R_1 represents a linear or branched alkyl radical having from 1 to 18 carbon atoms which is optionally substituted with one or more halogen atoms, a linear or branched alkenyl radical having from 1 to 18 carbon atoms, or a linear or branched alkynyl radical having from 1 to 18 carbon atoms, it being possible for this radical, in addition, to comprise one or more oxygen atoms and/or nitrogen atoms and/or sulphur atoms,

it being understood that:

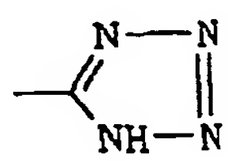
- when Y represents (b), then R_1 comprises a number of atoms of between 1 and 12 inclusive, and preferably of between 4 and 12 inclusive, and still more preferably between 6 and 12 inclusive,

- when Y represents (c), then R_1 comprises a number of atoms of between 1 and 10 inclusive, and preferably of between 4 and 10 inclusive, and still more preferably of between 6 and 10 inclusive,

- when Y is different from (b) and R_1 is an unsaturated radical or comprises a heteroatom, then the unsaturation and/or the heteroatom of R_1 cannot be at the α position with respect to Y,

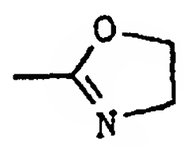
- R_2 represents:

(a) a tetrazolyl radical of formula



(b) a nitrile radical,

(c) an oxazolinyl radical of formula



(d) a $-CH_2OR_3$ radical,

(e) a $-CO-R_4$ radical,

R_3 and R_4 having the meanings given below,

- R_3 represents a hydrogen atom, a lower alkyl radical, a monohydroxyalkyl radical having from 1 to 6 carbon atoms, or a polyhydroxyalkyl radical having from 2 to 6 carbon atoms, a cycloaliphatic radical having from 3 to 6 carbon atoms, it being possible for R_3, in addition, to represent a tetrahydropyranyl radical,

- R_4 represents:

(a) a hydrogen atom,

(b) a lower alkyl radical,

(c) an -NR'(R") radical,

R' and R" having the meanings given below,

(d) an $-OR_5$ radical,

R_5 having the meaning given below,

$-R_5$ represents:

(a) a hydrogen atom,

(b) a linear or branched alkyl radical having from 1 to 18 carbon atoms,

(c) a monohydroxyalkyl radical having from 1 to 6 carbon atoms,

(d) a polyhydroxyalkyl radical having from 2 to 6 carbon atoms and comprising from 2 to 5 hydroxyl groups,

(e) an aryl radical,

(f) an aralkyl radical which is optionally substituted with:

- one or more linear or branched alkyl radicals having from 1 to 18 carbon atoms,
- one or more -CO-R"' radicals,
- one or more -O-R"' radicals,

R"' having the meaning given below,

- R' and R", which are identical or different, represent a hydrogen atom, a lower alkyl radical, an

alkenyl radical having from 3 to 4 carbon atoms, a cycloaliphatic radical having from 3 to 6 carbon atoms, an aryl or aralkyl radical which is (are) optionally substituted, an amino acid or amino sugar residue, or alternatively they can together form a heterocycle,

- R"' represents a hydrogen atom, or a linear or branched alkyl chain having from 1 to 18 carbon atoms.

The invention also relates to the salts of the compounds of formula (I) wherein R_2 represents a carboxylic acid function and the geometric and optical isomers of the said compounds of formula (I).

When the compounds according to the invention are provided in the form of addition salts with a base, they are salts of an alkali or alkaline-earth metal, or alternatively salts of zinc, magnesium or strontium, of an organic amine or the quaternary ammonium salts, when they contain at least one free acid function.

When the compounds of the invention are provided in the form of addition salts with an acid, they are pharmaceutically or cosmetically acceptable salts which are obtained by addition of an inorganic or organic acid, in particular hydrochloric, hydrobromic, sulphuric, acetic, citric, fumaric, hemisuccinic, maleic and mandelic acid.

According to the present invention, lower

alkyl radical is understood to mean a linear or branched radical having from 1 to 6 carbon atoms and, preferably, the methyl, ethyl, isopropyl, n-butyl, tert-butyl, pentyl or hexyl radicals.

Alkyl radical is understood to mean a linear or branched radical having from 1 to 18 carbon atoms which is optionally substituted with one or more halogen atoms. Among the halogen atoms, a fluorine, chlorine or bromine atom is preferred.

The alkyl radicals are preferably chosen from methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl, hexyl or 2-ethylhexyl, octyl, nonyl, decyl, dodecyl, dodecanyl, tetradecanyl or 3,3,4,4,5,5,6,6,7,-7,8,8,8-tridecafluorooctyl radicals.

Alkenyl radical is understood to mean a linear or branched radical having from 1 to 18 carbon atoms comprising one or more double bonds and preferably the allyl, butenyl, hexenyl, octenyl, decenyl, dodecenyl or tetradecenyl radicals.

Alkynyl radical is understood to mean a linear or branched radical having from 1 to 18 carbon atoms comprising one or more triple bonds and preferably the propynyl, butyn-2-yl, pentyn-2-yl, hexyn-2-yl, octyn-2-yn, decyn-2-yl or 2-dodecyn-2-yl radicals.

Monohydroxyalkyl radical is understood to mean a radical having from 1 to 6 carbon atoms, in particular a 2-hydroxyethyl, 2-hydroxypropyl or 3-hydroxypropyl radical.

Polyhydroxyalkyl radical is understood to mean a radical containing from 2 to 6 carbon atoms and from 1 to 5 hydroxyl groups, such as the 2,3-dihydroxypropyl, 2,3,4-trihydroxybutyl or 2,3,4,5-tetrahydroxypentyl radicals or a pentaerythritol residue.

Cycloaliphatic radical having from 3 to 6 carbon atoms is understood to mean preferably a cyclopropyl radical, a cyclopentyl radical or a cyclohexyl radical.

Aryl radical is understood to mean a phenyl radical, optionally substituted with at least one halogen, lower alkyl, hydroxyl, alkoxy, nitro function, polyether radical or amino function which is optionally protected with an acetyl group or which is optionally substituted with at least one lower alkyl.

Aralkyl radical is understood to mean a benzyl or phenethyl radical which are optionally substituted with at least one halogen, lower alkyl, hydroxyl, alkoxy, nitro function, polyether radical or amino function which is optionally protected with an

acetyl group or which is optionally substituted with at least one lower alkyl.

Amino acid residue is understood to mean a residue which is derived from one of the 20 amino acids of L or D configuration which constitute mammalian proteins, and it is preferably a residue which is derived from lysine, glycine or aspartic acid.

Amino sugar residue is understood to mean preferably those which are derived from glucosamine, galactosamine, mannosamine or meglumine.

Heterocycle is understood to mean preferably a piperidino, morpholino, pyrrolidino or piperazino radical which is optionally substituted at the 4-position with a C_1-C_6 alkyl or mono- or polyhydroxyalkyl radical as defined above.

Among the compounds of formula (I) above which fall within the scope of the present invention, there may be mentioned in particular:

- methyl 3,8-dithia-11,11,12,12,13,13,14,14,15,15,16,16,16-tridecafluoro-5-hexadecynoate,
- 3,8-dithia-11,11,12,12,13,13,14,14,15,15,16,16,16-tridecafluoro-5-hexadecynoic acid,
- methyl 3,8-dithia-5-docosynoate,
- 3,8-dithia-5-docosynoic acid,
- methyl 3,8-dithia-5-hexadecynoate,

- 3,8-dithia-5-hexadecynoic acid,
- 3-thia-5-hexadecynoic acid,
- methyl 3,8-dithia-5-heptadecynoate,
- 3,8-dithia-5-heptadecynoic acid,
- 3-thia-5,8-heptadecadiynoic acid,
- 3-thia-5,8-octadecadiynoic acid,
- 3-thia-5,8-pentadecadiynoic acid,
- 3-thia-5,8,11-octadecatriynoic acid,
- 3-thia-5-octadecaynoic acid,
- 3-thia-5,8,11-heptadecatriynoic acid,
- 3-thia-5-heptadecaynoic acid,
- 3-thia-5,8,11-hexadecatriynoic acid,
- 3-thia-5,8-hexadecadiynoic acid,
- 3-thia-5,8,11-pentadecatriynoic acid,
- 3-thia-5-pentadecaynoic acid,
- 3-thia-5-tetradecaynoic acid,
- 3-thia-5,8,11-heptadecatriynoic acid.

According to the present invention, the compounds of formula (I) which are more particularly preferred are those for which at least one of the, and preferably all of the, following conditions are fulfilled:

- R2 is a -CO-R4 radical,
- R4 is a hydroxyl radical,
- Y is chosen from

- the radical (c) and R1 is an alkyl radical having from 4 to 10 carbon atoms,

or the radical (a) in which t equals 0 and R1 is an alkyl radical having from 4 to 12 carbon atoms,

or the radical (b) and R1 is a fluorinated radical having from 4 to 12 carbon atoms,

The subject of the present invention is also the methods for preparing the compounds of formula (I), in particular according to the reaction schemes given in **Figures 1, 2, 3, 4, 5, 6 and 7.**

Thus, when Y corresponds to a methylene or to a triple bond, the compounds of formula (I) in accordance with the invention may be prepared using one of the two methods represented in **Figures 1 and 2.**

The first method (**Figure 1**) consists in preparing the anion of an alkyne of formula (1) with a strong base such as an alkyl halomagnesium and then in reacting it with an excess of 1,4-dihalobutyne to form the 1-halo-2,5-diyne derivative (2). Some alkynes are commercially available, such as for example 1-heptyne or 1-decyne. The other alkynes of formula R_1-C≡C-H are prepared by reacting sodium acetylide with the corresponding halide R_1-X.

The 2,5,8-triyne derivatives (4) are obtained

by reacting the derivative (2) with the dianion of propargyl alcohol. The triyne alcohol (3) thus obtained is converted to the corresponding halide to give the 1-halo-2,5,8-triyne derivative having the structure (4).

The alkyne halides (2) or (4) lead, upon treatment with the dianion of thioglycolic acid or with the thiolate of a mercaptan, to the compounds of the invention of formula (I) for which Y corresponds to a triple bond, R_1 being either a saturated alkyl radical or an alkyl radical comprising an unsaturation in particular a triple bond situated at the β position with respect to Y, or alternatively a perfluorinated alkyl radical.

The dianion of thioglycolic acid is formed by treating the latter with 2 equivalents of a base. The thiolate of a mercaptan is prepared with one equivalent of a base. This base is an inorganic or organic base, the preferred bases being sodium hydroxide, potassium hydroxide or sodium methoxide.

After reacting the dianion of thioglycolic acid with the alkyne halide, the 3-thiaalkynoic acid of formula (I) is purified by crystallization from an appropriate solvent when it is a solid at room temperature, or by chromatography on silica gel for a

compound which is liquid at this temperature. After reacting the anion of an alkyl mercaptan with the alkyne halide, the ester of the 3-thiaalkynoic acid obtained is generally purified by chromatography on a silica column.

The second method (**Figure 2**) consists in directly preparing alkyne intermediates whose triple bond is at the 2-position with respect to the function present at the end of the chain.

The "propyne motif" is grafted via propargyl alcohol onto an alkyl halide of formula 5 when the alcohol 6 is not commercially available. The alkynyl alcohol 6 is converted to the corresponding halide 7 when 7 is not commercially available. The extension of the chain is obtained by grafting the dianion of propargyl alcohol. The alcohol obtained is then converted to the corresponding halide 2 which may also be obtained according to Figure 1. This halide 2, when treated with the dianion of propargyl alcohol, leads to the alcohol 3 which is in turn converted to a halide 4.

For example, the preparation of 1-halo-2,5-tetradecadiyne is described in French patent 2,584,400.

The dianion of propargyl alcohol is prepared by treating this alcohol with 2 equivalents of a base. The bases used are strong bases such as organolithium

compounds such as for example n-butyllithium or organomagnesium compounds such as ethyl or propyl halomagnesium in an anhydrous solvent, preferably an ether such as tetrahydrofuran or diethyl ether. After reaction of this dianion and acidification of the reaction medium, the alkynyl alcohol is purified by distillation or recrystallization. This alcohol is treated in a chlorinated solvent such as dichloromethane or 1,2-dichloroethane, or an ether, with a phosphorus trihalide or a carbon tetrahalide, triphenylphosphine mixture. The alkyne halide thus obtained is purified, depending on its mode of preparation, by distillation (when its stability allows it), or by chromatography.

Thus, when Y corresponds to a sulphur atom, the compounds of formula (I) in accordance with the invention may be prepared using one of the two methods represented in Figures 3 and 4.

The first method (Figure 3) consists in preparing the compounds of the invention from the ester 8 obtained by reaction of the anion of alkyl thioglycolate such as methyl thioglycolate, which is reacted with 1,4-dichlorobutyne used in excess so as to promote the monosubstitution reaction. The halo ester 8 thus obtained is then reacted with the anions of the

mercaptans having the structure R_1-SH. These reactions are carried out in the customary dipolar solvents such as alcohols such as methanol or ethers such as tetrahydrofuran.

It is understood that the thiolate R_1S^- can react on an excess of 1,4-dichloro-2-butyne to form the alkyne R_1-S-CH_2-C≡C-CH_2-Cl which can in turn react with the dianion of thioglycolic acid or the thiolate of a mercaptan to form the derivatives having the structure (I) **(Figure 4)**.

The carboxylic acids having the structure (I) may be converted to the corresponding esters according to the customary methods for converting a carboxylic acid to an ester, that is to say by the reaction of an alcohol in an acidic medium or by the reaction for displacing the halogen from an alkyl halide with the sodium or potassium carboxylate function of the acid (I) or alternatively by reacting an activated form of the acids of formula (I) with an alcohol R_5-OH. Activated form is understood to mean the intermediate formed by addition, to an acid solution, of carbonyldiimidazole (CDI), dicyclohexylcarbodiimide (DCC) or any other reagent intended to form an activated form of acid, which is chosen from those known in the literature **(Figure 5)**.

Another route of preparation is to react the thiolate of an alkyl thioglycolate, treated with 1 equivalent of a base, with a halide of formula 2, 4 or 7.

The amides which fall within the definition of the general formula (I), in which R_2 designates the COR_4 group and R_4 the amino radical -NR'(R") in accordance with the invention, are obtained by reacting an activated form of the acids of formula (I) with an amine in an organic solvent. This activated form of the acid may be either an acid chloride, or an anhydride or alternatively the intermediate formed by the addition, to an acid solution, of carbonyldiimidazole (CDI), dicyclohexylcarbodiimide (DCC) or any other reagent intended to form an activated form of an acid, which is chosen from those known in the literature. The latter reaction is preferably carried out in a solvent medium such as dimethylformamide or alternatively a chlorinated solvent such as dichloromethane or 1,2-dichloroethane. This reaction takes place according to the reaction scheme given in Figure 6.

When the thioglycolamides are easily accessible, the amides may be directly obtained without proceeding via this acid of formula (I) by treating the halides 2, 4 or 7 with the thiolate formed beforehand

from the thioglycolamide 9. The latter is prepared by the action of an amine H-NR'(R") on ethyl thioglycolate $HS-CH_2-CO_2Et$ (Figure 7).

This method is in fact more simple. The halides 2, 4 or 7, on the one hand, and the potassium or sodium salt of the thioglycolamide 9, on the other hand, are prepared in methanol or ethanol. The halides 2, 4 or 7 are not purified and their reaction mixture is directly added to a solution of the thioglycolamide salified with 1 equivalent of a base.

The compounds of the invention exhibit properties of activation of the PPAR-type receptors. More particularly, the compounds of the invention exhibit properties of selective activation of the receptors of the PPAR-α subtype.

Activator of the PPAR-α-type receptors is understood to mean according to the invention any compound which exhibits in a transactivation test, as described in Kliewer et al., Nature 358, 771-774, 1992, an AC50 relative to PPAR-α of less than or equal to 10 μM. Preferably, the activator of the PPAR-α-type receptors exhibits an AC50 relative to PPAR-α of less than or equal to 3.5 μM and advantageously of less than or equal to 3 μM.

Preferably, the activator of the PPAR-α-type receptors is selective, that is to say that it exhibits a ratio R1 of AC50 relative to PPAR-α to the AC50 relative to the other subtypes of PPAR (PPAR-δ or PPAR-γ) of less than or equal to 10^{-1}. Preferably, R1 is less than or equal to 0.05, and more advantageously less than or equal to 0.02.

An AC50 is the concentration of "activator" compound necessary to exhibit 50% of the activity of a reference molecule. This activity is determined with the aid of a reporter enzyme (luciferase) for the activation due to the compound via one of the PPAR receptors, and more particularly of the PPAR-α type.

The activity of the PPAR-type receptors and more particularly of the PPAR-α subtypes has been the subject of many studies. All the references suggest a role for the PPAR-type receptors in the regulation of the metabolism and the homeostasis of lipids.

There may be mentioned, as a guide, the publication entitled "Differential Expression of Peroxisome Proliferator-Activated Receptor Subtypes During the Differentiation of Human Keratinocytes", Michel Rivier et al., J. Invest. Dermatol 111, 1998, p. 1116-1121, in which a large number of bibliographic references

relating to the PPAR-type receptors are listed.

The PPAR-α receptors are involved in the control of inflammation.

The use of the activators of the PPAR-α-type receptors to restore the barrier function, to promote differentiation and to inhibit epidermal proliferation has been described in international patent application WO 98/32444.

Furthermore, the use of the activators of the PPAR-α and/or PPAR-γ type receptors to treat skin disorders linked to an abnormality in the differentiation of the epidermal cells has been described in the publication by Michel Rivier et al., J. Invest. Dermatol 111, 1998, p 1116-1121.

The skin disorders linked to an abnormality in the differentiation of the epidermal cells are in particular psoriasis, eczema, lichen planus, skin lesions associated with a lupus, dermatites such as atopic, seborrhoeic or solar dermatites, keratoses such as seborrhoeic, senile, actinic, photoinduced or follicular keratosis, acne vulgaris, keloids, nevi, verrucas, ichtyoses and skin cancers.

The compounds of formula (I) according to the invention find application in the cosmetic field, in particular in body and hair hygiene and more

particularly for regulating the metabolism of cutaneous lipids, for the treatment of skins which are prone to acne, for combating the greasy appearance of the skin or of the hair, or in the treatment of physiologically dry skins.

The use of at least one compound of formula (I) also makes it possible to restore the skin barrier function and/or to promote differentiation and to inhibit epidermal proliferation. Compared with previously known products, these compounds of formula (I) have the advantage of exhibiting, furthermore, other advantageous properties, in particular anti-inflammatory or soothing properties, which makes them compounds which are less irritant and therefore better tolerated.

The present invention therefore relates to a cosmetic composition containing, in a cosmetically acceptable carrier, at least one compound of formula (I), one of its optical or geometric isomers or one of its salts, this composition being provided in particular in the form of a cream, a milk, a lotion, a gel, of lipid or polymeric microspheres or nanospheres or vesicles, of a soap or a shampoo.

The concentration of compound of formula (I) in the cosmetic compositions is between 0.0001 and 3%

by weight, preferably between 0.001 and 1% by weight, relative to the total weight of the composition.

The subject of the present invention is also, as a medicament, the compounds of formula (I) as described above.

The compounds according to the invention are particularly well-suited to the following fields of treatment:

1) dermatological conditions linked to an abnormality in the differentiation of the epidermal cells and in particular psoriasis, eczema, lichen planus, skin lesions associated with a lupus, dermatites such as atopic, seborrhoeic or solar dermatites, keratoses such as seborrhoeic, senile, actinic, photoinduced or follicular keratosis, acne vulgaris, keloids, nevi, verrucas, ichtyoses and skin cancers;

2) inflammatory conditions exhibiting no keratinization disorder, such as arthritis.

The subject of the present invention is also pharmaceutical compositions containing at least one compound of formula (I) as defined above, one of its optical or geometric isomers or one of its salts.

The subject of the present invention is also a pharmaceutical composition intended in particular for the treatment of the abovementioned conditions,

characterized in that it comprises, in a pharmaceutically acceptable carrier, at least one compound of formula (I), one of its optical or geometric isomers, or one of its salts.

Other characteristics, aspects, objects and advantages of the invention will emerge even more clearly on reading the description which follows, as well as various concrete examples, but not at all limiting, which are intended to illustrate it.

The administration of the composition according to the invention may be carried out by the enteral, parenteral or topical route. Preferably, the pharmaceutical composition is packaged in a form appropriate for application by the topical route.

For enteral administration, the composition, more particularly the pharmaceutical composition, may be provided in the form of tablets, gelatin capsules, sugar-coated tablets, syrups, suspensions, solutions, powders, granules, emulsions, lipid or polymeric microspheres or nanospheres or vesicles allowing a controlled release. For parenteral administration, the composition may be provided in the form of solutions or suspensions for infusion or for injection.

The compounds are used according to the invention are generally administered in a daily dose of

about 0.001 mg/kg to 100 mg/kg of body weight in 1 to 3 doses.

For topical administration, the pharmaceutical composition according to the invention is more particularly intended for the treatment of the skin and of the mucous membranes and may be provided in the form of ointments, creams, milks, pomades, powders, impregnated packs, solutions, gels, sprays, lotions or suspensions. It may also be provided in the form of lipid or polymeric microspheres or nanospheres or vesicles or of polymeric patches and of hydrogels allowing controlled release. This composition for topical administration may be provided either in anhydrous form, or in aqueous form.

The compounds are used by the topical route at a concentration which is generally of between 0.001% and 10% by weight, preferably between 0.01 and 1% by weight, relative to the total weight of the composition.

The compositions as described above may of course, in addition, contain inert or even pharmacodynamically active additives or combinations of these additives, and in particular: wetting agents, depigmenting agents such as hydroquinone, azelaic acid, caffeic acid or kojic acid; emollients; moisturizing agents such as

glycerol, PEG 400, thiamorpholinone and its derivatives or alternatively urea; antiseborrhoeic or anti-acne agents such as S-carboxylmethylcystein, S-benzylcysteamine, their salts or their derivatives, or benzoyl peroxide; antifungal agents such as ketoconazole or 4,5-polymethylene-3-isothiazolidones; antibacterials, carotenoids and, in particular, β-carotene; antipsoriatic agents such as anthraline and its derivatives; 5,8,11,14-eicosatetraynoic and 5,8,11-eicosatriynoic acids, their esters and amides and finally retinoids.

These compositions may also contain taste-enhancing agents, preservatives such as para-hydroxybenzoic acid esters, stabilizing agents, moisture-regulating agents, pH-regulating agents, osmotic pressure-modifying agents, emulsifying agents, UV-A and UV-B screening agents, antioxidants such as α-tocopherol, butylated hydroxyanisole or butylated hydroxytoluene.

Of course, persons skilled in the art will be careful to choose the possible compound(s) to be added to these compositions so that the advantageous properties intrinsically attached to the present invention are not or not substantially altered by the addition envisaged.

Several examples of production of active compounds of formula (I) according to the invention, as well as various concrete formulations based on such compounds, will now be given, by way of illustration and with no limitation being implied. In the text which follows or in the preceding text, the percentages are given by weight unless otherwise stated.

The various products of this invention are prepared from halogenated intermediates whose preparation is described in Examples 1, 6, 9, 13, 16, 18 and 20.

Example 1:

Preparation of methyl 7-chloro-3-thia-5-heptynoate

4.22 ml of a 30% solution of sodium methoxide in methanol are added dropwise (so that the temperature does not exceed 15°C) to a solution of 2 ml of methyl thioglycolate in 20 ml of methanol at 10°C, under an inert atmosphere. The mixture is kept stirring for 30 min and then added to a solution of 6.1 ml of 1,4-dichloro-2-butyne in 25 ml of methanol, under an inert atmosphere. The mixture is kept stirring for 6 hours at room temperature and then the reaction medium is poured over 100 ml of acid water (98 ml of water + 2 ml of concentrated H_2SO_4) and then extracted 3 times with

ethyl ether. The combined organic phases are washed 3 times with water and then with a saturated aqueous solution of NaCl before being dried (Na_2SO_4), filtered and concentrated under vacuum in a rotary evaporator. The 1,4-dichloro-2-butyne in excess in the oil thus obtained is removed by distillation under reduced pressure. The oily distillation residue obtained is chromatographed on a silica gel column (CH_2Cl_2) giving two grams of methyl 7-chloro-3-thia-5-heptynoate in the form of a pale yellow oil (yield 65%).

^{1}H NMR 200 MHz $CDCl_3$: 3.39 (s, 2H), 3.44 (t, 2H), 3.73 (s, 3H), 4.15 (t, 2H).

^{13}C NMR 50 MHz $CDCl_3$: 20.16, 30.45, 32.41, 52.42, 78.25, 81.67, 170.28.

$$Cl\text{-}CH_2\text{-}C{\equiv}C\text{-}CH_2\text{-}S\text{-}CH_2\text{-}CO_2Me$$

Example 2:

Preparation of methyl 3,8-dithia-11,11,12,12,13,13,14,14,15,15,16,16,16-tridecafluoro-5-hexadecynoate

1.5 ml of a 30% solution of sodium methoxide in methanol are added dropwise to a solution of 3.02 g of Foralkyl EM6 in 30 ml of methanol, under an inert atmosphere. The mixture is kept stirring for 30 min and

then added to a solution of 1.53 g of methyl 7-chloro-3-thia-5-heptynoate in 10 ml of methanol, under an inert atmosphere. The mixture is kept stirring for 12 hours at room temperature and then for 2 hours at 50°C and then the reaction medium is poured over 100 ml of acid water (98 ml of water + 2 ml of concentrated H_2SO_4) and then extracted 3 times with ethyl ether. The combined organic phases are washed 3 times with water and then with a saturated aqueous solution of NaCl before being dried (Na_2SO_4), filtered and concentrated under vacuum in a rotary evaporator. The oil thus obtained is chromatographed on a silica gel column (CH_2Cl_2/heptane 60/40) giving 2.3 grams of methyl 3,8-dithia-11,11,12,12,13,13,14,14,15,15,16,16,16-tridecafluoro-5-hexadecynoate in the form of a pale yellow oil (yield 73.5%).

^{1}H NMR 200 MHz $CDCl_3$: 2.30-2.56 (m, 2H), 2.95-2.86 (m, 2H), 3.34 (t, 2H), 3.39 (s, 2H), 3.43 (t, 2H), 3.74 (s, 3H).

^{13}C NMR 50 MHz $CDCl_3$: 19.87, 20.29, 22.24, 31.17, 31.61, 32.05, 32.37, 52.34, 78.61, 170.31 (only 1 acetylenic C atom, fluorine-carrying C atoms not out).

$$C_6F_{13}-CH_2-CH_2-S-CH_2-C\equiv C-CH_2-S-CH_2-CO_2Me$$

Example 3:

Preparation of 3,8-dithia-11,11,12,12,13,13,14,14,15,15,16,16,16-tridecafluoro-5-hexadecynoic acid

The acid is prepared by saponification of the methyl 3,8-dithia-11,11,12,12,13,13,14,14,15,15,16,16,16-tridecafluoro-5-hexadecynoate ester and purified by rapid chromatography on a short silica gel column (CH_2Cl_2/MeOH). The acid is thus isolated in the form of a beige wax with a yield of 87%.

^{1}H NMR 200 MHz $CDCl_3$: 2.20-2.60 (m, 2H), 2.85-2.93 (m, 2H), 3.34 (t, 2H), 3.42 (s, 2H), 3.46 (t, 2H).

Elemental analysis:	C	H	S	F
Calculated	32.19	2.12	12.28	47.28
Found	32.32	2.11	12.36	47.27

C_6F_{13}-CH_2-CH_2-S-CH_2-C≡C-CH_2-S-CH_2-CO_2H

Example 4:

Preparation of methyl 3,8-dithia-5-docosynoate

460 µl of a 30% solution of sodium methoxide in methanol are added to a solution of 665 µl of tetradecanethiol in a 5 ml methanol/2 ml THF mixture,

under an inert atmosphere. The mixture is kept stirring for 30 min and then 0.47 g of methyl 7-chloro-3-thia-5-heptynoate in 5 ml of methanol is added, under an inert atmosphere. The mixture is kept stirring for 8 hours at room temperature and then the reaction medium is poured over 100 ml of acid water (98 ml of water + 2 ml concentrated H_2SO_4) and then extracted 3 times with ethyl ether. The combined organic phases are washed 3 times with water and then with a saturated aqueous solution of NaCl before being dried (Na_2SO_4), filtered and concentrated under vacuum in a rotary evaporator. The wax thus obtained is chromatographed on a silica gel column (CH_2Cl_2) giving 1.05 g of methyl 3,8-dithia-5-docosynoate in the form of an oil. (Quantitative yield).

^{1}H NMR 200 MHz $CDCl_3$: 0.88 (s, 3H), 1.15-1.50 (m, 22H), 1.50-1.75 (m, 2H), 2.66 (t, 2H), 2.28 (m, 2H), 3.42 (s, 2H), 3.43-3.47 (m, 4H), 3.75 (s, 3H).

^{13}C NMR 50 MHz $CDCl_3$: 14.08, 19.71, 20.63, 22.68, 28.87, 29.09, 29.24, 29.34, 29.53, 29.61, 29.67, 31.81, 31.92, 32.55, 52.40, 77.53, 80.08, 170.47.

$C_{14}H_{29}$-S-CH_2-C≡C-CH_2-S-CH_2-CO_2Me

Example 5:

Preparation of 3,8-dithia-5-docosynoic acid

The acid is prepared by saponification of the methyl 3,8-dithia-5-docosynoate ester and purified by recrystallization from boiling heptane. 3,8-dithia-5-docosynoic acid is thus isolated in the form of a white solid with a yield of 81.5%.

^{1}H NMR 200 MHz $CDCl_3$: 0.87 (t, 3H), 1.15-1.46 (m, 22H), 1.46-1.76 (m, 2H), 2.65 (t, 2H), 3.28 (s, 2H), 3.46 (m, 4H).

^{13}C NMR 50 MHz $CDCl_3$: 14.01, 19.53, 20.55, 22.58, 28.76, 28.92, 29.14, 29.25, 29.44, 29.56, 31.68, 31.81, 32.27, 80.34, 175.73.

Elemental analysis:

	C	H	O	S
Calculated	64.47	9.74	8.59	17.21
Found	64.09	9.64	9.24	17.06

$C_{14}H_{29}-S-CH_2-C\equiv C-CH_2-S-CH_2-CO_2H$

Example 6:

Preparation of 1-chloro-5-thia-2-tridecyne

6.46 ml of a 30% solution of sodium methoxide in methanol are added dropwise to a solution of 5 g of octanethiol in 60 ml of methanol, under an inert

atmosphere. The mixture is kept stirring for 30 min, with stirring, and then added to 9.35 ml of 1,4-dichloro-2-butyne in 70 ml of methanol, under an inert atmosphere. The mixture is kept stirring for 12 hours at room temperature and then the reaction medium is poured over 100 ml of acid water (98 ml of water + 2 ml concentrated H_2SO_4) and then extracted 3 times with ethyl ether. The combined organic phases are washed 3 times with water and then with a saturated aqueous solution of NaCl before being dried (Na_2SO_4), filtered and concentrated under vacuum in a rotary evaporator. The 1,4-dichloro-2-butyne in excess in the oil thus obtained is removed by distillation under reduced pressure. The oily distillation residue obtained is chromatographed on a silica gel column (CH_2Cl_2) giving 7.5 g of 1-chloro-5-thia-2-tridecyne in the form of a pale yellow oil (yield 94%).

^{1}H NMR 200 MHz $CDCl_3$: 0.82 (s, 3H), 1.1-1.3 (m, 10H), 1.30-1.65 (m, 2H), 2.65 (t, 2H), 3.22 (t, 2H), 4.15 (t, 2H).

^{13}C NMR 50 MHz $CDCl_3$: 14.21, 19.62, 19.83, 22.77, 28.93, 29.11, 29.30, 30.87, 31.92, 77.45, 83.25.

C_8H_{17}-S-CH_2-C≡C-CH_2-Cl

Example 7:

Preparation of methyl 3,8-dithia-5-hexadecynoate

2.03 ml of a 30% solution of sodium methoxide in methanol are added dropwise (so that the temperature does not exceed 15°C) to a solution of 980 µl of methyl thioglycolate in 10 ml of methanol at 10°C, under an inert atmosphere. The mixture is kept stirring for 30 min and then added to a solution of 2.5 g of 1-chloro-5-thia-2-tridecyne in a mixture of 7 ml of methanol with 3 ml of THF under an inert atmosphere. The mixture is kept stirring for 15 hours at room temperature and then the reaction medium is poured over 100 ml of acid water (98 ml of water + 2 ml concentrated H_2SO_4) and then extracted 3 times with ethyl ether. The combined organic phases are washed 3 times with water and then with a saturated aqueous solution of NaCl before being dried (Na_2SO_4), filtered and concentrated under vacuum in a rotary evaporator. The oily residue obtained is chromatographed on a silica gel column (CH_2Cl_2) giving 2.3 grams of methyl 3,8-dithia-5-hexadecynoate in the form of a pale orange-coloured oil (yield 71%).

^{1}H NMR 200 MHz $CDCl_3$: 0.81 (t, 3H), 0.90-1.50 (m, 10H),

1.50-1.61 (m, 2H), 2.62 (t, 2H), 3.25 (t, 2H), 3.39 (s, 2H), 3.41 (t, 2H), 3.72 (s, 3H).

^{13}C NMR 50 MHz $CDCl_3$: 14.0, 19.53, 20.47, 22.54, 28.75, 28.92, 29.08, 31.61, 31.70, 32.35, 52.35, 77.38, 79.91, 170.38.

C_8H_{17}-S-CH_2-C≡C-CH_2-S-CH_2-CO_2Me

Example 8:

Preparation of 3,8-dithia-5-hexadecynoic acid

The acid is prepared by saponification of the methyl 3,8-dithia-5-hexadecynoate ester and purified by recrystallization from boiling heptane and then from diisopropyl ether. 3,8-dithia-5-hexadecynoic acid is thus isolated in the form of a beige solid with a yield of 67%.

^{1}H NMR 200 MHz $CDCl_3$: 0.84 (t, 3H), 1.1-1.45 (m, 10H), 1.45-1.7 (m, 2H), 2.62 (t, 2H), 3.25 (t, 2H), 3.41 (s, 2H), 3.43 (t, 2H).

^{13}C NMR 50 MHz $CDCl_3$: 14.09, 19.61, 20.63, 22.64, 28.84, 29.00, 29.17, 31.76, 32.35, 80.55, 176.01.

Elemental analysis:	C	H	O	S
Calculated	58.29	8.39	11.09	22.23
Found	58.57	8.44	11.26	21,94

$C_8H_{17}-S-CH_2-C\equiv C-CH_2-S-CH_2-CO_2H$

Example 9:

Preparation of 1-bromo-2-tridecyne

1-Bromo-2-tridecyne (colourless oil) is prepared from 2-tridecyn-1-ol using the CBr_4/triphenylphosphine mixture in dichloromethane to carry out the halogenation. 1-Bromo-2-tridecyne (colourless oil) is thus formed with a yield of 91%.

^1H NMR 200 MHz $CDCl_3$: 0.84 (t, 3H), 1.15-1.57 (m, 16H), 2.20 (t.t, 2H), 3.89 (t, 2H).

$C_{10}H_{21}-C\equiv C-CH_2-Br$

Example 10:

Preparation of 3-thia-5-hexadecynoic acid

2.20 ml of a 30% solution of sodium methoxide in methanol are added dropwise to a solution of 422 µl of thioglycolic acid in 5 ml of methanol, under an inert atmosphere. The mixture is kept stirring for 30 min and then added to a solution of 1.5 g of 1-bromo-2-tridecyne in 10 ml of methanol, under an inert atmosphere. The mixture is kept stirring for 15 hours at room temperature and then the reaction medium is

poured over 100 ml of acid water (98 ml of water + 2 ml concentrated H_2SO_4) and then extracted 3 times with ethyl ether. The combined organic phases are washed 3 times with water and then with a saturated aqueous solution of NaCl before being dried (Na_2SO_4), filtered and concentrated under vacuum in a rotary evaporator. The oily residue obtained crystallizes on cooling. The 3-thia-5-hexadecynoic acid is recrystallized from heptane and then from diisopropyl ether and isolated in the form of white flakes with a yield of 25%.

^{1}H NMR 200 MHz $CDCl_3$: 0.87 (t, 3H), 1.1-1.65 (m, 16H), 2.19 (m, 2H), 3.42 (t, 2H), 3.46 (s, 2H).

^{13}C NMR 50 MHz $CDCl_3$: 14.11, 18.78, 20.81, 22.68, 28.72, 28.89, 29.12, 29.31, 29.54, 31.90, 32.31, 74.16, 85.04, 175.44.

Elemental analysis:

	C	H	O	S
Calculated	66.62	9.69	11.83	11.86
Found	66.77	9.64	12.05	

$C_{10}H_{21}-C\equiv C-CH_2-S-CH_2-CO_2H$

Example 11:

Preparation of methyl 3,8-dithia-5-heptadecynoate

2 ml of a 30% solution of sodium methoxide in methanol are added to a solution of 2 ml of nonanethiol in a

20 ml methanol/5 ml THF mixture, under an inert atmosphere. The mixture is kept stirring for 30 min and then added to a solution of 2 g of methyl 7-chloro-3-thia-5-heptynoate in 20 ml of methanol, under an inert atmosphere. The mixture is kept stirring for 15 hours at room temperature and then the reaction medium is poured over 100 ml of acid water (98 ml of water + 2 ml concentrated H_2SO_4) and then extracted 3 times with ethyl ether. The combined organic phases are washed 3 times with water and then with a saturated aqueous solution of NaCl before being dried (Na_2SO_4), filtered and concentrated under vacuum in a rotary evaporator. The oil thus obtained is chromatographed on a silica gel column (CH_2Cl_2/heptane 85/15) giving 2.1 g of methyl 3,8-dithia-5-heptadecynoate in the form of an orange-coloured oil (yield 64%).

^{1}H NMR 200 MHz $CDCl_3$: 0.83 (t, 3H), 1.0-1.65 (m, 14H), 2.64 (t, 2H), 3.26 (t, 2H), 3.39 (s, 2H), 3.42 (t, 2H), 3.73 (s, 3H).

^{13}C NMR 50 MHz $CDCl_3$: 14.11, 19.64, 20.58, 22.66, 28.85, 29.02, 29.25, 29.48, 31.71, 31.86, 32.46, 52.46, 77.47, 80.02, 170.50.

C_9H_{19}-S-CH_2-C≡C-CH_2-S-CH_2-CO_2Me

Example 12:

Preparation of 3,8-dithia-5-heptadecynoic acid

The acid is prepared by saponification of the methyl 3,8-dithia-5-heptadecynoate ester and purified by recrystallization from diisopropyl ether. 3,8-dithia-5-heptadecynoic acid is thus isolated in the form of a white solid with a yield of 44%.

^{1}H NMR 200 MHz $CDCl_3$: 0.84 (t, 3H), 1.1-1.45 (m, 12H), 1.45-1.7 (m, 2H), 2.65 (t, 2H), 3.27 (t, 2H), 3.44 (s, 2H), 3.46 (t, 2H).

^{13}C NMR 50 MHz $CDCl_3$: 14.10, 19.60, 20.62, 22.65, 28.83, 28.99, 29.22, 29.46, 31.74, 31.90, 32.35, 80.41, 176.10.

Elemental analysis:	C	H	O	S
Calculated	59.56	8.66	10.58	21.20
Found	59.75	8.70	10.42	20.96

C_9H_{19}-S-CH_2-C≡C-CH_2-S-CH_2-CO_2H

Example 13:

Preparation of 1-chloro-2,5-tetradecadiyne

38 ml of a 1M solution of ethyl magnesium bromide in THF are added dropwise, at room temperature, to a

solution of 5 grams of 1-decyne in 15 ml of anhydrous THF, under an inert atmosphere. With the addition complete, the mixture is kept stirring for 30 min at room temperature and then heated under reflux for 1 h 30 min. The mixture is cooled to room temperature and then 286 mg of copper(I) chloride are added and the mixture is again heated under reflux for 1 hour. It is then cooled to between 40 and 50°C and 12.5 g of 1,4-dichloro-2-butyne dissolved in 25 ml of anhydrous THF are added. The mixture is refluxed for 1 hour and then kept stirring for 15 h at room temperature before heating again under reflux for 2 h. The reaction medium is then cooled to 4°C and hydrolysed with care with a saturated aqueous solution of NH_4Cl. The medium is then extracted 3 times with diethyl ether and the combined organic phases are washed 3 times with water and then with a saturated aqueous solution of NaCl before being dried over Na_2SO_4, filtered and concentrated under vacuum in a rotary evaporator. The oily residue containing 1,4-dichloro-2-butyne in excess is purified by distillation under reduced pressure to give 1-chloro-2,5-tetradecadiyne (b.p. = 111-114°C, 0.36 mbar) in the form of an orange-coloured oil (yield 52.4%).

^{1}H NMR 200 MHz $CDCl_3$: 0.87 (t, 3H), 1.1-1.5 (m, 12H), 2.13 (t.t, 2H), 3.19 (m, 2H), 4.11 (t, 2H).

^{13}C NMR 50 MHz $CDCl_3$: 9.92, 14.05, 18.62, 22.62, 28.62, 28.84, 29.06, 19.14, 30.68, 31.79, 72.68, 74.87, 81.39, 81.71.

$$C_8H_{17}-C\equiv C-CH_2-C\equiv C-CH_2-Cl$$

Example 14:

Preparation of 3-thia-5,8-heptadecadiynoic acid

2.02 ml of a 30% solution of sodium methoxide in methanol are added dropwise to a solution of 372 µl of thioglycolic acid in 5 ml of methanol, under an inert atmosphere. The mixture is kept stirring for 30 min and then a solution of 1.2 g of 1-chloro-2,5-tetradecadiyne in 6 ml of methanol is added under an inert atmosphere. The mixture is kept stirring for 20 hours at room temperature and then the reaction medium is poured over 100 ml of acid water (98 ml of water + 2 ml concentrated H_2SO_4) and then extracted 3 times with ethyl ether. The combined organic phases are washed 3 times with water and then with a saturated aqueous solution of NaCl before being dried (Na_2SO_4), filtered and concentrated under vacuum in a rotary evaporator. The oily residue obtained crystallizes on cooling.

3-Thia-5,8-heptadecadiynoic acid is recrystallized from

heptane and then from hexane and finally from diisopropyl ether. The acid is thus isolated in the form of beige crystals with a yield of 49.4%.

^{1}H NMR 200 MHz $CDCl_3$: 0.84 (t, 3H), 1.05-1.50 (m, 12H), 2.13 (m, 2H), 3.17 (m, 2H), 3.42 (t, 2H), 3.45 (t, 2H), 9.75 (broad s, 1H).

^{13}C NMR 50 MHz $CDCl_3$: 9.88, 14.08, 18.66, 20.53, 22.64, 28.68, 28.88, 29.09, 29.17, 31.82, 32.36, 73.32, 74.62, 79.13, 81.17, 176.21.

Elemental analysis:	C	H	O	S
Calculated	68.53	8.63	11.41	11.43
Found	67.88	8.59	12.02	12.21

$C_8H_{17}-C\equiv C-CH_2-C\equiv C-CH_2-S-CH_2-CO_2H$

Example 15:

Preparation of 3-thia-5,8-heptadecadiyn-1-ol

1.06 ml of a 30% solution of sodium methoxide in methanol are added dropwise, at room temperature, to a solution of 374 µl of 2-mercaptoethanol in 5 ml of anhydrous methanol, under an inert atmosphere. The mixture is kept stirring for 30 min and then added to a solution of 1.2 g of 1-chloro-2,5-tetradecadiyne in 6 ml of methanol, under an inert atmosphere. The

mixture is kept stirring for 15 hours at room temperature and then the reaction medium is poured over 100 ml of acid water (98 ml of water + 2 ml concentrated H_2SO_4) and then extracted 3 times with ethyl ether. The combined organic phases are washed 3 times with water and then with a saturated aqueous solution of NaCl before being dried (Na_2SO_4), filtered and concentrated under vacuum in a rotary evaporator. The oil thus obtained crystallizes on cooling. It is purified by recrystallization from a heptane/pentane mixture and then from a heptane/pentane/diisopropyl ether mixture. 3-Thia-5,8-heptadecadiyn-1-ol is thus isolated in the form of pale yellow flakes with a yield of 61%.

^{1}H NMR 200 MHz $CDCl_3$: 0.86 (t, 3H), 1.1-1.6 (m, 12H), 2.12 (m, 2H), 2.89 (t, 2H), 3.15 (m, 2H), 3.26 (t, 2H), 3.78 (t, 2H).

^{13}C NMR 50 MHz $CDCl_3$: 9.84, 14.06, 18.63, 19.39, 22.61, 28.65, 28.85, 29.06, 29.14, 31.79, 34.84, 60.24, 73.36, 75.86, 78.24, 81.10.

$C_8H_{17}-C\equiv C-CH_2-C\equiv C-CH_2-S-CH_2-CH_2-OH$

Example 16:

Preparation of 1-chloro-2,5-pentadecadiyne

34.5 ml of a 1M solution of ethyl magnesium bromide in THF are added dropwise, at room temperature, to a solution of 5 grams of 1-undecyne in 15 ml of anhydrous THF, under an inert atmosphere. With the addition complete, the mixture is kept stirring for 30 min at room temperature and then heated under reflux for 1 h 30 min. The mixture is cooled to room temperature and then 260 mg of copper(I) chloride are added and the mixture is again heated under reflux for 1 hour. The mixture is then cooled to room temperature and 11.3 g of 1,4-dichloro-2-butyne are added fairly rapidly. The mixture is refluxed for 1 h 30 min and then kept stirring for 15 h at room temperature before heating again under reflux for 3 h. The reaction medium is then cooled to 4°C and hydrolysed with care with a saturated aqueous solution of NH_4Cl. The medium is then extracted 3 times with diethyl ether and the combined organic phases are washed 3 times with water and then with a saturated aqueous solution of NaCl before being dried over Na_2SO_4, filtered and concentrated under vacuum in a rotary evaporator. The oily residue containing 1,4-dichloro-2-butyne in excess is purified by distillation under reduced pressure to give 1-chloro-2,5-

pentadecadiyne in the form of a colourless oil with a yield of 37.8%.

^{1}H NMR 200 MHz $CDCl_3$: 0.87 (t, 3H), 1.1-1.55 (m, 14H), 2.14 (m, 2H), 3.19 (m, 2H), 4.13 (t, 2H).

^{13}C NMR 50 MHz $CDCl_3$: 9.96, 14.10, 18.66, 22.66, 28.64, 28.86, 29.13, 29.27, 29.47, 30.73, 31.86, 72.67, 74.91, 80.86, 81.76.

$$C_9H_{19}-C\equiv C-CH_2-C\equiv C-CH_2-Cl$$

Example 17:

Preparation of 3-thia-5,8-octadecadiynoic acid

3.2 ml of a 30% solution of sodium methoxide in methanol are added dropwise to a solution of 611 µl of thioglycolic acid in 7 ml of methanol, under an inert atmosphere. The mixture is kept stirring for 30 min and then a solution of 2 g of 1-chloro-2,5-pentadecadiyne in 20 ml of methanol is added under an inert atmosphere. The mixture is kept stirring for 20 hours at room temperature and then the reaction medium is poured over 100 ml of acid water (98 ml of water + 2 ml concentrated H_2SO_4) and then extracted 3 times with ethyl ether. The combined organic phases are washed 3 times with water and then with a saturated aqueous solution of NaCl before being dried (Na_2SO_4), filtered

and concentrated under vacuum in a rotary evaporator. The oily residue obtained crystallizes on cooling. 3-Thia-5,8-octadecadiynoic acid is recrystallized from diisopropyl ether and thus isolated in the form of a white solid with a yield of 26%.

^{1}H NMR 200 MHz $CDCl_3$ 0.87 (t, 3H), 1.1-1.6 (m, 14H), 2.13 (t.t, 2H), 3.17 (m, 2H), 3.42 (t, 2H), 3.45 (s, 2H), 10.78 (broad s, 1H).

^{13}C NMR 50 MHz $CDCl_3$: 9.87, 14.10, 18.65, 20.52, 22.66, 28.67, 29.13, 29.26, 29.46, 31.85, 32.35, 73.30, 74.62, 79.11, 81.16, 176.25.

Elemental analysis:	C	H	O	S
Calculated	69.34	8.90	10.87	10.89
Found	69.17	8.91	10.70	10.66

$C_9H_{19}-C\equiv C-CH_2-C\equiv C-CH_2-S-CH_2-CO_2H$

Example 18:

Preparation of 1-chloro-2,5-dodecadiyne

38.1 ml of a 1M solution of ethyl magnesium bromide in THF are added dropwise, at room temperature, to a solution of 4 grams of 1-octyne in 15 ml of anhydrous THF, under an inert atmosphere. With the addition complete, the mixture is kept stirring for 30 min at

room temperature and then heated under reflux for 1 h 30 min. The mixture is cooled to room temperature and then 287 mg of copper(I) chloride are added and the mixture is again heated under reflux for 1 hour. The mixture is then cooled to room temperature and 9.95 ml of 1,4-dichloro-2-butyne dissolved in 20 ml of anhydrous THF are rapidly added dropwise. The mixture is kept stirring for 30 min at room temperature, then it is heated under reflux for 2 h and then it is kept stirring for 15 h at room temperature before being heated under reflux for another 2 h. The reaction medium is then cooled to 4°C and hydrolysed with care with a saturated aqueous solution of NH_4Cl. The medium is then extracted 3 times with diethyl ether and the combined organic phases are washed 3 times with water and then with a saturated aqueous solution of NaCl before being dried over Na_2SO_4, filtered and concentrated under vacuum in a rotary evaporator. The oily residue containing 1,4-dichloro-2-butyne in excess is purified by distillation under reduced pressure and 1-chloro-2,5-dodecadiyne is isolated in the form of a pale yellow oil (yield 36%).

^1H NMR 200 MHz $CDCl_3$: 0.88 (t, 3H), 1.1-1.5 (m, 8H), 2.14 (t.t, 2H), 3.20 (m, 2H), 4.13 (t, 2H).

^{13}C NMR 50 MHz $CDCl_3$: 9.97, 14.04, 18.66, 22.53, 28.53, 28.60, 30.74, 31.31, 72.71, 74.89, 81.46, 81.76.

$C_6H_{13}-C\equiv C-CH_2-C\equiv C-CH_2-Cl$

Example 19:

Preparation of 3-thia-5,8-pentadecadiynoic acid

3.85 ml of a 30% solution of sodium methoxide in methanol are added dropwise to a solution of 742 µl of thioglycolic acid in 8 ml of methanol, under an inert atmosphere. The mixture is kept stirring for 30 min and then a solution of 2 g of 1-chloro-2,5-dodecadiyne in 20 ml of methanol is added under an inert atmosphere. The mixture is kept stirring for 15 hours at room temperature and then the reaction medium is poured over 100 ml of acid water (98 ml of water + 2 ml concentrated H_2SO_4) and then extracted 3 times with ethyl ether. The combined organic phases are washed 3 times with water and then with a saturated aqueous solution of NaCl before being dried (Na_2SO_4), filtered and concentrated under vacuum in a rotary evaporator. The oily residue obtained crystallizes at cold temperature. 3-Thia-5,8-pentadecadiynoic acid is recrystallized from diisopropyl ether.

$C_6H_{13}-C\equiv C-CH_2-C\equiv C-CH_2-S-CH_2-CO_2H$

Example 20:

Preparation of 1-chloro-2,5-undecadiyne

54.6 ml of a 1M solution of ethyl magnesium bromide in THF are added dropwise, at room temperature, to a solution of 5 grams of 1-heptyne in 15 ml of anhydrous THF, under an inert atmosphere. With the addition complete, the mixture is kept stirring for 30 min at room temperature and then heated under reflux for 1 h 30 min. The mixture is cooled to room temperature and then 412 mg of copper(I) chloride are added and the mixture is again heated under reflux for 1 hour. The mixture is then cooled to room temperature and 14.2 ml of 1,4-dichloro-2-butyne are added fairly rapidly. The mixture is refluxed for 1 h 30 min and then kept stirring for 15 h at room temperature before heating again under reflux for 2 h 30 min. The reaction medium is then cooled to 4°C and hydrolysed with care with a saturated aqueous solution of NH_4Cl. The medium is then extracted 3 times with diethyl ether and the combined organic phases are washed 3 times with water and then with a saturated aqueous solution of NaCl before being dried over Na_2SO_4, filtered and concentrated under vacuum in a rotary evaporator. The oily residue

containing 1,4-dichloro-2-butyne in excess is purified by distillation under reduced pressure to give 6.55 g of 1-chloro-2,5-undecadiyne in the form of a pale yellow oil (yield 69%).

^{1}H NMR 200 MHz $CDCl_3$: 0.88 (t, 3H), 1.1-1.5 (m, 6H), 2.13 (t.t, 2H), 3.19 (m, 2H), 4.13 (t, 2H).

^{13}C NMR 50 MHz $CDCl_3$: 9.92, 13.94, 18.58, 22.17, 28.32, 30.71, 31.02, 72.68, 74.86, 81.38, 81.72.

$$C_5H_{11}-C\equiv C-CH_2-C\equiv C-CH_2-Cl$$

Example 21:

Preparation of 3-thia-5,8,11-heptadecatriynoic acid

This synthesis is carried out in four stages:

- The first stage consists in preparing, from commercially available heptyne, 1-chloro-2,5-undecadiyne by condensation of 1,4-dichlorobutyne (see Example 20).
- In the second stage, 2,5,8-tetradecatriynol is obtained by the reaction of the dianion of propargyl alcohol with 1-choro-2,5-undecadiyne.
- In the third stage, the 2,5,8-tetradecatriynol is converted to the corresponding bromide by the action of phosphorus tribromide.

- Finally, in the fourth stage, this bromide is reacted with the dianion of thioglycolic acid.

a) Preparation of 2,5,8-tetradecatriynol

The dianion of propargyl alcohol is prepared by exchanging acidic protons (alcohol and acetylenic) with propylmagnesium chloride. A dilute solution of 4.8 cm^3 of propargyl alcohol (0.082 mole) diluted with 10 cm^3 of anhydrous THF is added dropwise to a suspension containing 2.1 equivalents of propylmagnesium chloride stirred at 0° under an inert atmosphere in 100 cm^3 of THF. This organomagnesium compound (0.17 mole) is prepared by reacting 14 cm^3 of chloropropane with 4.2 g of magnesium in THF.

Once the emission of propane has ceased, the temperature is allowed to rise up to 20°C and then the mixture is heated to the boiling temperature of the solvent for 1 h 30 min. 0.7 g of copper(I) cyanide which is gradually solubilized in the medium is then added. A clear solution is obtained and then, at a temperature of 50°C, 15 g of 1-chloro-2,5-undecadiyne (0.082 mole) diluted with 10 cm^3 of THF are added to this dianion and then the mixture is heated, with stirring, for 3 hours at the boiling temperature of the solvent - and then abandoned at room temperature

overnight.

The reaction mixture is then slowly poured into 200 cm^3 of a 1 N aqueous solution of sulphuric acid, and then extracted 3 times with 100 cm^3 of ethyl acetate. The organic phases are combined, washed with the aid of an ammonium chloride solution, dried over magnesium sulphate and then the ethyl acetate is removed. The crude 2,5,8-tetradecatriynol is dissolved in 150 cm^3 of boiling heptane.

The solution is then filtered and then cooled to -20°C. The crystals formed are rapidly drained and dried. 7 g of 2,5,8-tetradecatriynol are thus obtained in the form of beige crystals.

$$C_5H_{11}-C\equiv C-CH_2-C\equiv C-CH_2-C\equiv C-CH_2OH$$

b) Preparation of 1-bromo-2,5,8-tetradecatriyne

The alcohol obtained above is directly converted to the corresponding bromide by adding 2 cm^3 of phosphorus tribromide (0.0216 mole) to this alcohol diluted in 50 cm^3 of ethyl ether. This stirred mixture under an inert atmosphere and protected from light is heated to the boiling temperature of the solvent for 2 hours and then washed at room temperature with the aid of a saturated aqueous solution of ammonium chloride.

The organic phase is decanted off and then dried over magnesium sulphate. Three hours later, the magnesium sulphate is removed by filtration. The filtrate containing 1-bromo-2,5,8-tetradecatriyne is used directly in the next stage.

$$C_5H_{11}-C\equiv C-CH_2-C\equiv C-CH_2-C\equiv C-CH_2Br$$

c) Preparation of 3-thia-5,8,11-heptadecatriynoic acid

A solution containing 0.0346 mole of the dianion of thioglycolic acid is added, with stirring and under an inert atmosphere, to the filtrate thus obtained. This dianion being prepared beforehand by treating, at room temperature and under an inert atmosphere, 2.4 cm^3 of thioglycolic acid (0.0346 mole) dissolved in 50 cm^3 of methanol with 4.2 g of sodium methoxide (0.076 mole).

One hour after the addition of this dianion to the solution containing 1-bromo-2,5,8-tetradecatriyne, the latter is completely converted.

The reaction mixture is poured into a solution of 350 cm^3 of ice-cold 1 N sulphuric acid. The mixture is extracted 3 times with ethyl ether. The ethereal phases are washed with water, dried over sodium sulphate and then concentrated. The crude

3-thia-5,8,11-heptadecatriynoic acid thus obtained in the form of a viscous liquid is dissolved in 100 cm^3 of isopropyl ether. Animal charcoal is added to the solution obtained, the mixture is stirred for a quarter of an hour at room temperature and then filtered. The filtrate is concentrated to about 40 cm^3 and heptane is added until cloudiness appears. The mixture is then cooled to -5°C. The crystals formed are rapidly filtered, dried and stored at 0°C. 3 g of 3-thia-2,5,8-heptadecatriynoic acid having a beige colour are obtained.

The ^1H and ^{13}C NMR spectra are consistent with the structure.

^1H NMR 80 MHz $CDCl_3$: 0.80 (t, 3H), 1.1-1.65 (m, 6H), 2.15 (t.t., 2H), 3.16 (s, 4), 3.44 (s, 4H), 10.0-11.0 (unresolved complex, H).

^{13}C NMR 100 MHz $CDCl_3$: 9.76, 9.95, 14.00, 18.67, 20.52, 22.22, 28.42, 31.08, 32.48, 73.55, 73.75, 75.09, 75.21, 78.33, 81.06, 176.47.

$C_5H_{11}-C\equiv C-CH_2-C\equiv C-CH_2-C\equiv C-CH_2-S-CH_2-CO_2H$

Example 22:

In this example, various concrete formulations based on the compounds according to the invention have been illustrated.

A - ORAL ROUTE

(a) 0.2 g tablet

- compound of Example 2	0.001 g
- starch	0.114 g
- dicalcium phosphate	0.020 g
- silica	0.020 g
- lactose	0.030 g
- talc	0.010 g
- magnesium stearate	0.005 g

(b) Oral suspension in 5 ml ampoules

- compound of Example 3	0.001 g
- glycerine	0.500 g
- sorbitol at 70%	0.500 g
- sodium saccharinate	0.010 g
- methyl para-hydroxybenzoate	0.040 g
- flavouring qs	
- purified water qs	5 ml

(c) 0.8 g tablet

- compound of Example 5	0.500 g
- pregelatinized starch	0.100 g
- microcrystalline cellulose	0.115 g
- lactose	0.075 g
- magnesium stearate	0.010 g

(d) Oral suspension in 10 ml ampoules

- compound of Example 15	0.05 g
- glycerine	1.000 g
- sorbitol at 70%	1.000 g
- sodium saccharinate	0.010 g
- methyl para-hydroxybenzoate	0.080 g
- flavouring qs	
- purified water qs	10 ml

B - <u>TOPICAL ROUTE</u>

(a) Ointment

- compound of Example 10	0.020 g
- isopropyl myristate	81.700 g
- fluid liquid paraffin	9.100 g
- silica ("Aerosil 200" sold by DEGUSSA)	9.180 g

(b) Ointment

- compound of Example 8 0.300 g
- petroleum jelly 100 g

(c) Nonionic water-in-oil cream

- compound of Example 7 0.100 g
- mixture of emulsifying lanolin alcohols, of waxes and of oils ("anhydrous eucerin" sold by BDF) 39.900 g
- methyl para-hydroxybenzoate 0.075 g
- propyl para-hydroxybenzoate 0.075 g
- sterile demineralized water qs 100 g

(d) Lotion

- compound of Example 4 0.100 g
- polyethylene glycol (PEG 400) 69.900 g
- ethanol at 95% 30.000 g

(e) Hydrophobic ointment

- compound of Example 14 0.300 g
- isopropyl mirystate 36.400 g
- silicone oil ("Rhodorsil 47 V 300" sold by RHONE-POULENC) 36.400 g
- beeswax 13.600 g
- silicone oil ("Abil 300,000 cst" sold by GOLDSCHMIDT) 100 g

(f) Nonionic oil-in-water cream

- compound of Example 4	0.500 g
- cetyl alcohol	4.000 g
- glyceryl monostearate	2.500 g
- PEG 50 stearate	2.500 g
- shea butter	9.200 g
- propylene glycol	2.000 g
- methyl para-hydroxybenzoate	0.075 g
- propyl para-hydroxybenzoate	0.075 g
- sterile demineralized water	100 g

Example 23

Several of the results of biological tests of the compounds of the invention, as well as of comparative examples, have been illustrated in this example.

The biological tests carried out correspond to those described in the application. The method used to determine the AC50 values is that described in Kliewer et al., Nature 358, 771-774, 1992. Thus, the activating power via PPAR-α, PPAR-γ or PPAR-δ of molecules can be evaluated with a transactivation test in which HeLa cells were cotransfected with an expression vector encoding these receptors and a reporter plasmid containing a PPRE response element cloned upstream of a

portion of a promoter of the SV40 virus and of the luciferase gene. The cotransfected cells are treated for 24 hours with the molecules to be tested and the activity of the luciferase is determined by luminescence.

Reference 1, reference molecule for the PPAR-α receptors is [4-chloro-6-(2,3-dimethylphenylamino)pyrimidin-2-ylsulphanyl]acetic acid;

Reference 2, reference molecule for the PPAR-δ and PPAR-γ receptors is 5-{4-[2-(methylpyridin-2-ylamino)ethoxy]benzyl}thiazolidine-2,4-dione;

Comparative Examples 1 and 2 are unsaturated fatty acids of the thiaeicosa(poly)ynoic type which are obtained from European patent application EP 342115.

Comparative Example 1 is 3-thia-5,8,11,14-eicosatetraynoic acid.

Comparative Example 2 is 3-thia-5,8,11-eicosatriynoic acid.

The results obtained in the tests for transactivation of the PPAR-type receptors are assembled in the following table:

Compounds	α		γ		δ	
	Ymax%	AC50μM	Ymax%	AC50μM	Ymax%	AC50μM
Reference 1	100	1.4	n.a.	n.a.	n.a.	n.a.
Reference 2	n.a.	n.a.	100	0.07	100	0.13
Example 8	91	2.9	n.a.	n.a.	n.a.	n.a.
Example 10	142	1.5	n.a.	n.a.	n.a.	n.a.
Example 14	116	1	n.a.	n.a.	n.a.	n.a.
Example 21	138	3	n.a.	n.a.	n.a.	n.a.
Comparative Example 1	128	4	83	3	125	7
Comparative Example 2	112	5	58	4	74	11

n.a. means not active

These results show the selective activation of the compounds of the invention for the PPAR-α-type receptors.

These results also show that unsaturated fatty acids of the thiaeicosa(poly)ynoic type, obtained from European patent application EP 342115, do not exhibit this property of selective activation of the PPAR-α-type receptors.

For the purposes of this specification it will be clearly understood that the word "comprising" means "including but not limited to", and that the word "comprises" has a corresponding meaning.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. (Poly)thiaalkynoic compounds, characterized in that they correspond to the following formula (I):

$$R_1\text{-}Y\text{-}CH_2\text{-}C{\equiv}C\text{-}CH_2\text{-}S\text{-}CH_2\text{-}R_2 \qquad (I)$$

in which:

-Y represents:

(a) an -S(O)t radical,

t is an integer equal to 0, 1 or 2,

(b) a $-CH_2-$ radical,

(c) a $-C{\equiv}C-$ radical,

(d) a $-C{=}C-$ radical,

- R_1 represents a linear or branched alkyl radical having from 1 to 18 carbon atoms which is optionally substituted with one or more halogen atoms, a linear or branched alkenyl radical having from 1 to 18 carbon atoms, or a linear or branched alkynyl radical having from 1 to 18 carbon atoms, it being possible for this radical, in addition, to comprise one or more oxygen atoms and/or nitrogen atoms and/or sulphur atoms,

it being understood that:

- when Y represents (b), then R_1 comprises a number of atoms of between 1 and 12 inclusive, and preferably

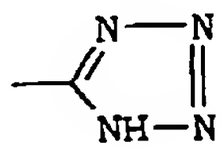
of between 4 and 12 inclusive, and still more preferably between 6 and 12 inclusive,

- when Y represents (c), then R_1 comprises a number of atoms of between 1 and 10 inclusive, and preferably of between 4 and 10 inclusive, and still more preferably of between 6 and 10 inclusive,

- when Y is different from (b) and R_1 is an unsaturated radical or comprises a heteroatom, then the unsaturation and/or the heteroatom of R_1 cannot be at the α position with respect to Y,

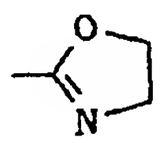
- R_2 represents:

(a) a tetrazolyl radical of formula



(b) a nitrile radical,

(c) an oxazolinyl radical of formula



(d) a $-CH_2OR_3$ radical,

(e) a $-CO-R_4$ radical,

R_3 and R_4 having the meanings given below,

- R_3 represents a hydrogen atom, a lower alkyl radical, a monohydroxyalkyl radical having from 1 to 6

carbon atoms, or a polyhydroxyalkyl radical having from 2 to 6 carbon atoms, a cycloaliphatic radical having from 3 to 6 carbon atoms, it being possible for R_3, in addition, to represent a tetrahydropyranyl radical,

- R_4 represents:

(a) a hydrogen atom,

(b) a lower alkyl radical,

(c) an $-NR'(R'')$ radical,

R' and R'' having the meanings given below,

(d) an $-OR_5$ radical,

R_5 having the meaning given below,

- R_5 represents:

(a) a hydrogen atom,

(b) a linear or branched alkyl radical having from 1 to 18 carbon atoms,

(c) a monohydroxyalkyl radical having from 1 to 6 carbon atoms,

(d) a polyhydroxyalkyl radical having from 2 to 6 carbon atoms and comprising from 2 to 5 hydroxyl groups,

(e) an aryl radical,

(f) an aralkyl radical which is optionally substituted with:

- one or more linear or branched alkyl

radicals having from 1 to 18 carbon atoms,

- one or more -CO-R"' radicals,

- one or more -O-R"' radicals,

R"' having the meaning given below,

- R' and R", which are identical or different, represent a hydrogen atom, a lower alkyl radical, an alkenyl radical having from 3 to 4 carbon atoms, a cycloaliphatic radical having from 3 to 6 carbon atoms, an aryl or aralkyl radical which is (are) optionally substituted, an amino acid or amino sugar residue, or alternatively they can together form a heterocycle,

- R"' represents a hydrogen atom, or a linear or branched alkyl chain having from 1 to 18 carbon atoms,

and the optical and geometric isomers of the said compounds of formula (i) as well as their salts.

2. Compounds according to Claim 1, characterized in that they are provided in the form of salts of an alkali or alkaline-earth metal, of zinc, of an organic amine or of an inorganic or organic acid.

3. Compounds according to either of Claims 1 and 2, characterized in that the lower alkyl radicals are chosen from the methyl, ethyl, isopropyl, n-butyl, tert-butyl, pentyl or hexyl radicals.

4. Compounds according to one of the preceding claims, characterized in that the linear or

branched alkyl radicals having from 1 to 18 carbon atoms which are optionally substituted with one or more halogen atoms are chosen from the methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl, hexyl or 2-ethylhexyl, octyl, nonyl, decyl, dodecyl, dodecanyl, tetradecanyl or 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl radicals.

5. Compounds according to one of the preceding claims, characterized in that the linear or branched alkenyl radicals having from 1 to 18 carbon atoms are chosen from the allyl, butenyl, hexenyl, octenyl, decenyl, dodecenyl or tetradecenyl radicals.

6. Compounds according to one of the preceding claims, characterized in that the linear or branched alkynyl radicals having from 1 to 18 carbon atoms are chosen from the propynyl, butyn-2-yl, pentyn-2-yl, hexyn-2-yl, octyn-2-yn, decyn-2-yl or 2-dodecyn-2-yl radicals.

7. Compounds according to one of the preceding claims, characterized in that the monohydroxyalkyl radicals having from 1 to 6 carbon atoms are chosen from the 2-hydroxyethyl, 2-hydroxypropyl or 3-hydroxypropyl radicals.

8. Compounds according to one of the preceding claims, characterized in that the

polyhydroxyalkyl radicals having from 2 to 6 carbon atoms are chosen from the 2,3-dihydroxypropyl, 2,3,4-trihydroxybutyl or 2,3,4,5-tetrahydroxypentyl radicals or the pentaerythritol residue.

9. Compounds according to one of the preceding claims, characterized in that the aryl radicals correspond to a phenyl radical, optionally substituted with at least one halogen, lower alkyl, hydroxyl, alkoxy, nitro function, polyether radical or amino function which is optionally protected with an acetyl group or which is optionally substituted with at least one lower alkyl.

10. Compounds according to one of the preceding claims, characterized in that the aralkyl radicals are chosen from the benzyl or phenethyl radical which are optionally substituted with at least one halogen, lower alkyl, hydroxyl, alkoxy, nitro function, polyether radical or amino function which is optionally protected with an acetyl group or which is optionally substituted with at least one lower alkyl.

11. Compounds according to one of the preceding claims, characterized in that the cycloaliphatic radicals having from 3 to 6 carbon atoms are chosen from a cyclopropyl radical, a cyclopentyl radical or a cyclohexyl radical.

12. Compounds according to any one of the preceding claims, characterized in that the amino acid residues are chosen from the group consisting of residues which are derived from lysine, glycine or aspartic acid.

13. Compounds according to any one of the preceding claims, characterized in that the amino sugar residues are chosen from the group consisting of the residues which are derived from glucosamine, galactosamine, mannosamine or meglumine.

14. Compounds according to any one of the preceding claims, characterized in that the heterocyclic radicals are chosen from the group consisting of the piperidino, morpholino, pyrrolidino or piperazino radicals which are optionally substituted at the 4-position with a C_1-C_6 alkyl radical or with a mono- or polyhydroxyalkyl.

15. Compounds according to Claim 1, characterized in that they are taken, alone or in the form of mixtures, from the group consisting of:

- methyl 3,8-dithia-11,11,12,12,13,13,14,14,15,15,16,16,16-tridecafluoro-5-hexadecynoate,
- 3,8-dithia-11,11,12,12,13,13,14,14,15,15,16,16,16-tridecafluoro-5-hexadecynoic acid,
- methyl 3,8-dithia-5-docosynoate,

- 3,8-dithia-5-docosynoic acid,
- methyl 3,8-dithia-5-hexadecynoate,
- 3,8-dithia-5-hexadecynoic acid,
- 3-thia-5-hexadecynoic acid,
- methyl 3,8-dithia-5-heptadecynoate,
- 3,8-dithia-5-heptadecynoic acid,
- 3-thia-5,8-heptadecadiynoic acid,
- 3-thia-5,8-octadecadiynoic acid,
- 3-thia-5,8-pentadecadiynoic acid,
- 3-thia-5,8,11-octadecatriynoic acid,
- 3-thia-5-octadecaynoic acid,
- 3-thia-5,8,11-heptadecatriynoic acid,
- 3-thia-5-heptadecaynoic acid,
- 3-thia-5,8,11-hexadecatriynoic acid,
- 3-thia-5,8-hexadecadiynoic acid,
- 3-thia-5,8,11-pentadecatriynoic acid,
- 3-thia-5-pentadecaynoic acid,
- 3-thia-5-tetradecaynoic acid,
- 3-thia-5,8,11-heptadecatriynoic acid.

16. Compounds according to Claim 1, characterized in that they exhibit one at least one of the, and preferably all of the, following characteristics:

- R2 is a -CO-R4 radical,
- R4 is a hydroxyl radical,

- Y is chosen from

- the radical (c) and R1 is an alkyl radical having from 4 to 10 carbon atoms,

or the radical (a) in which t equals 0 and R1 is an alkyl radical having from 4 to 12 carbon atoms,

or the radical (b) and R1 is an alkyl radical substituted with one or more fluorine atoms having from 4 to 12 carbon atoms,

17. Cosmetic composition, characterized in that it comprises, in a cosmetically acceptable carrier, at least one of the compounds as defined in any one of Claims 1 to 16.

18. Composition according to Claim 17, characterized in that the concentration of compound(s) according to one of Claims 1 to 16 is between 0.0001% and 3% by weight relative to the whole composition.

19. Use of a cosmetic composition as defined in either of Claims 17 and 18 for body and hair hygiene and more particularly for regulating the metabolism of cutaneous lipids, for the treatment of skins which are prone to acne, for combating the greasy appearance of the skin or of the hair, or in the treatment of physiologically dry skins.

20. Use of a cosmetic composition as defined

in either of Claims 17 and 18 to improve the skin barrier function or promote differentiation and inhibit epidermal proliferation.

21. Compounds according to any one of Claims 1 to 16 as a medicament.

22. Use of a compound according to any one of Claims 1 to 16 for the manufacture of a medicament intended for the treatment of dermatological conditions linked to an abnormality in the differentiation of the epidermal cells and in particular psoriasis, eczema, lichen planus, skin lesions associated with a lupus; of dermatites such as atopic, seborrhoeic or solar dermatites; of keratoses such as seborrhoeic, senile, actinic, photoinduced or follicular keratosis; of acne vulgaris, keloids, nevi, verrucas, ichtyoses and skin cancers; or of inflammatory conditions exhibiting no keratinization disorder, such as arthritis.

23. Pharmaceutical composition, characterized in that it comprises, in a pharmaceutically acceptable carrier, at least one of the compounds as defined in any one of Claims 1 to 16.

24. Composition according to Claim 23, characterized in that the concentration of compound(s) according to one of Claims 1 to 16 is between 0.001% and 10% by weight relative to the whole composition.

Dated this 22nd day of March 2000
L'ORÉAL
By their Patent Attorneys: GRIFFITH HACK
Fellows Institute of Patent and Trade Mark Attorneys of Australia

Figure 1

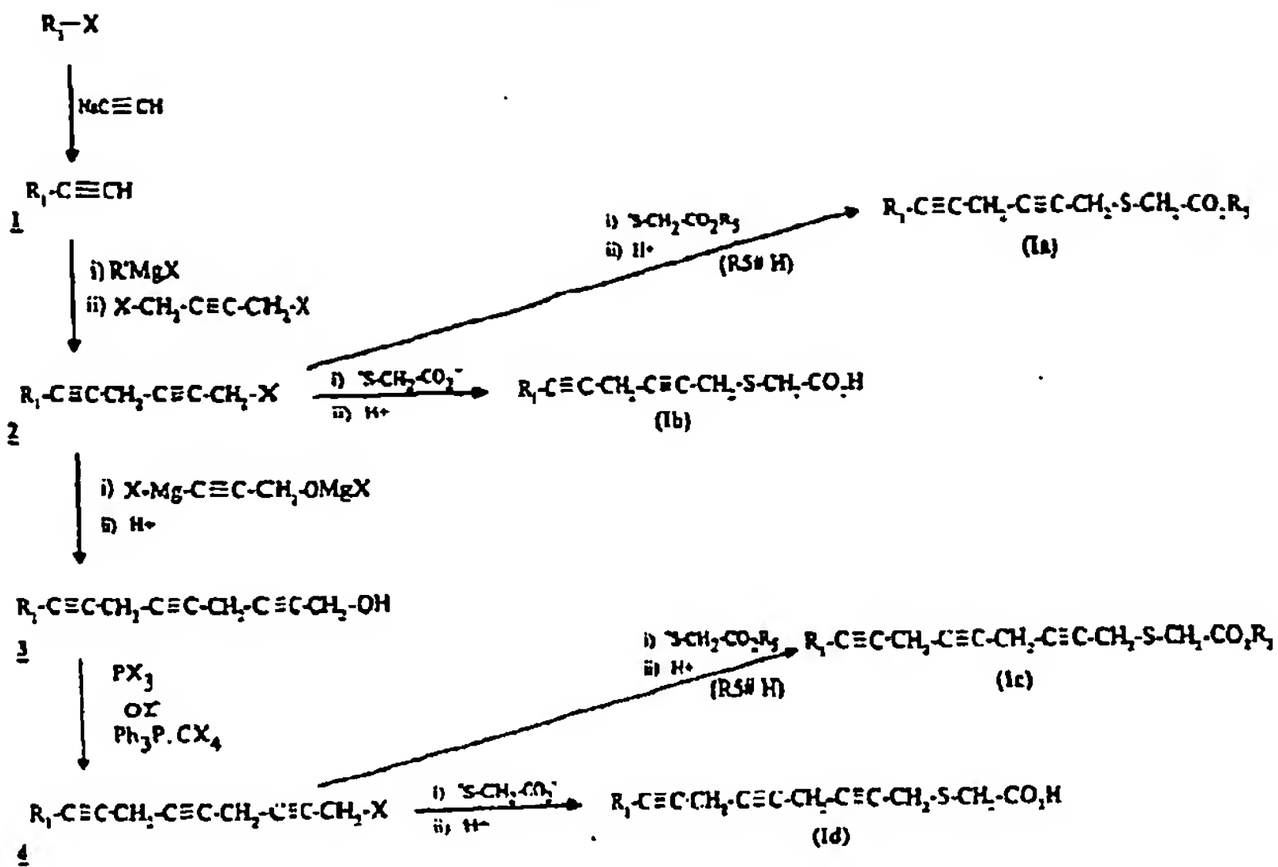

R1—X
NaC≡CH
R1-C≡CH
1
i) R'MgX
ii) X-CH2-C≡C-CH2-X
R1-C≡C-CH2-C≡C-CH2-X
2
i) 'S-CH2-CO2-
ii) H+
R1-C≡C-CH2-C≡C-CH2-S-CH2-CO2H
(Ib)
i) 'S-CH2-CO2R3
ii) H+
(RS# H)
R1-C≡C-CH2-C≡C-CH2-S-CH2-CO2R3
(Ia)
i) X-Mg-C≡C-CH2-OMgX
ii) H+
R1-C≡C-CH2-C≡C-CH2-C≡C-CH2-OH
3
PX3
or
Ph3P.CX4
R1-C≡C-CH2-C≡C-CH2-C≡C-CH2-X
4
i) 'S-CH2-CO2-
ii) H+
R1-C≡C-CH2-C≡C-CH2-C≡C-CH2-S-CH2-CO2H
(Id)
i) 'S-CH2-CO2R3
ii) H+
(RS# H)
R1-C≡C-CH2-C≡C-CH2-C≡C-CH2-S-CH2-CO2R3
(Ic)

Figure 2

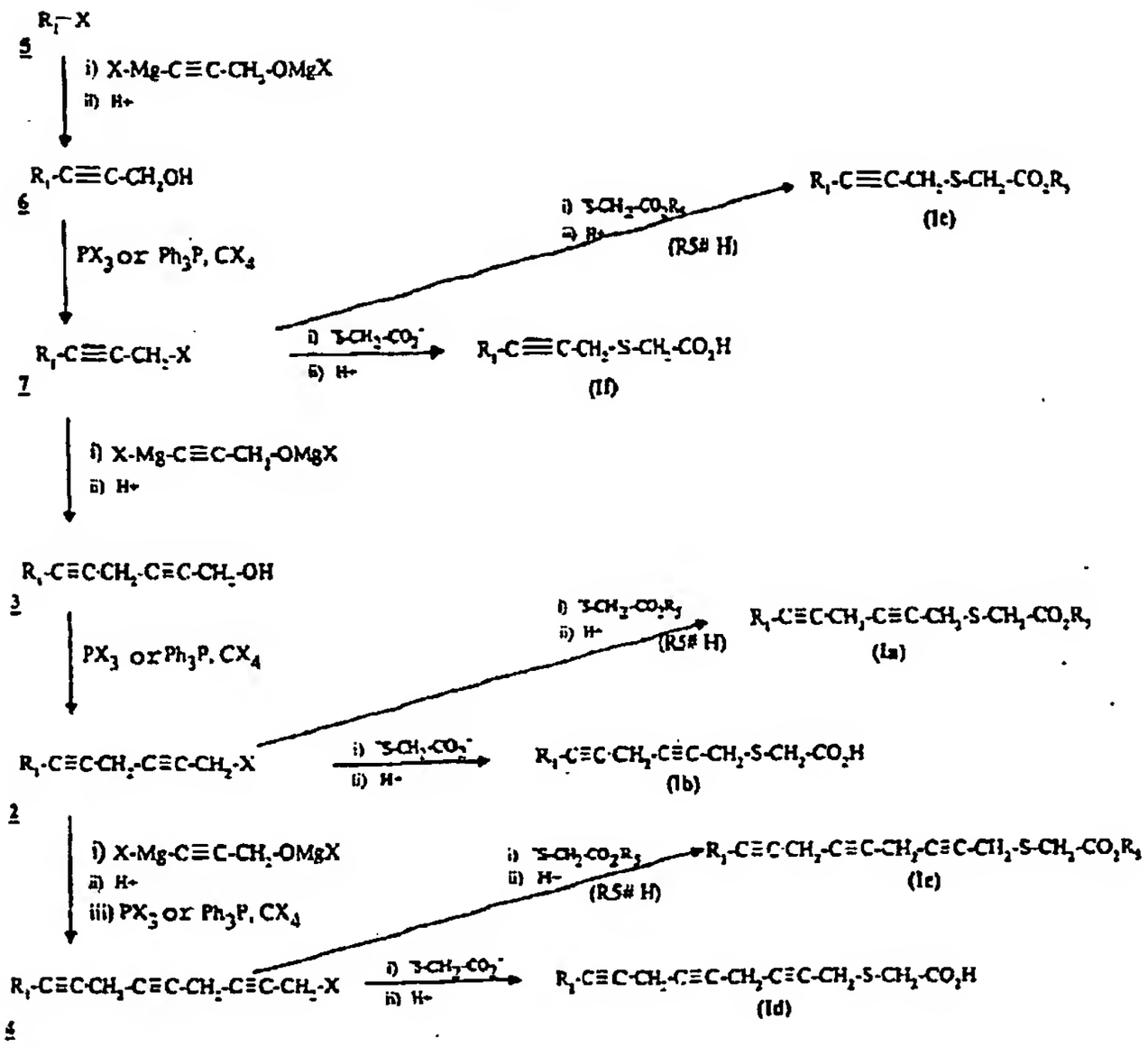
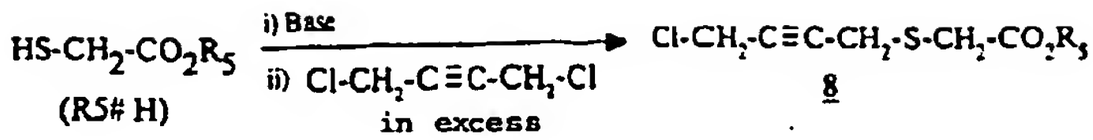

R1-X
5
i) X-Mg-C≡C-CH2-OMgX
ii) H+
R1-C≡C-CH2OH
6
PX3 or Ph3P, CX4
R1-C≡C-CH2-X
7
i) -S-CH2-CO2-
ii) H+
R1-C≡C-CH2-S-CH2-CO2H
(If)
i) -S-CH2-CO2R3
ii) H+
(RS# H)
R1-C≡C-CH2-S-CH2-CO2R3
(Ie)
i) X-Mg-C≡C-CH2-OMgX
ii) H+
R1-C≡C-CH2-C≡C-CH2-OH
3
PX3 or Ph3P, CX4
R1-C≡C-CH2-C≡C-CH2-X
2
i) -S-CH2-CO2-
ii) H+
R1-C≡C-CH2-C≡C-CH2-S-CH2-CO2H
(Ib)
i) -S-CH2-CO2R3
ii) H+
(RS# H)
R1-C≡C-CH2-C≡C-CH2-S-CH2-CO2R3
(Ia)
i) X-Mg-C≡C-CH2-OMgX
ii) H+
iii) PX3 or Ph3P, CX4
R1-C≡C-CH2-C≡C-CH2-C≡C-CH2-X
4
i) -S-CH2-CO2-
ii) H+
R1-C≡C-CH2-C≡C-CH2-C≡C-CH2-S-CH2-CO2H
(Id)
i) -S-CH2-CO2R3
ii) H+
(RS# H)
R1-C≡C-CH2-C≡C-CH2-C≡C-CH2-S-CH2-CO2R3
(Ic)

figure 3


HS-CH2-CO2R5
(R5≠ H)
i) Base
ii) Cl-CH2-C≡C-CH2-Cl
in excess
Cl-CH2-C≡C-CH2-S-CH2-CO2R5
8

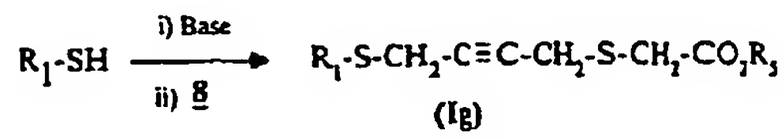

R1-SH
i) Base
ii) 8
R1-S-CH2-C≡C-CH2-S-CH2-CO2R5
(Ig)

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figure 4

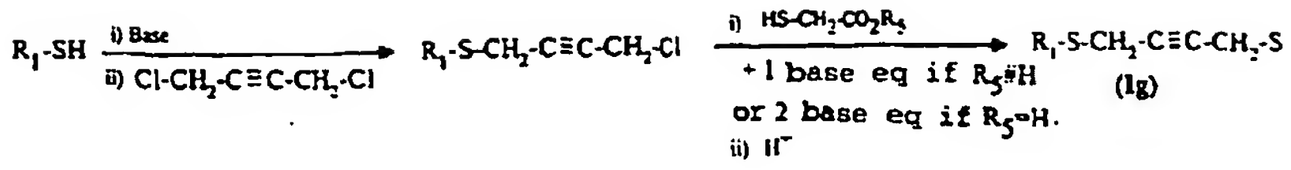
R_1-SH
i) Base
ii) Cl-CH_2-C≡C-CH_2-Cl
R_1-S-CH_2-C≡C-CH_2-Cl
i) HS-CH_2-CO_2R_5
+ 1 base eq if R_5≠H
or 2 base eq if R_5=H.
ii) H^+
R_1-S-CH_2-C≡C-CH_2-S
(Ig)

Figure 5

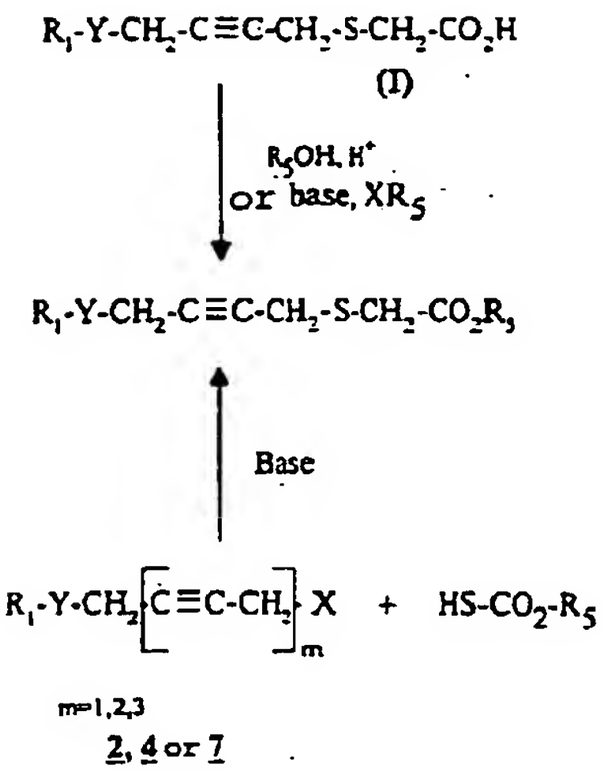
R1-Y-CH2-C≡C-CH2-S-CH2-CO2H
(I)
R5OH, H+
or base, XR5
R1-Y-CH2-C≡C-CH2-S-CH2-CO2R5
Base
R1-Y-CH2-[C≡C-CH2]m-X + HS-CO2-R5
m=1,2,3
2, 4 or 7

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Figure 6

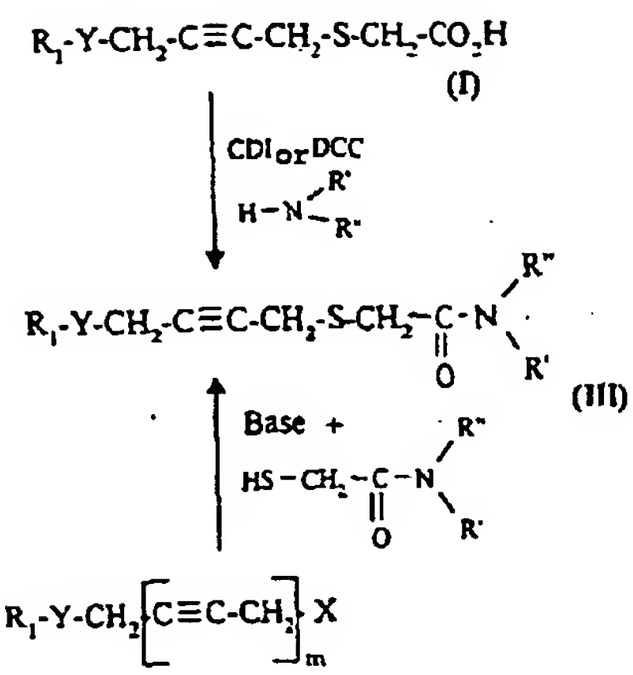
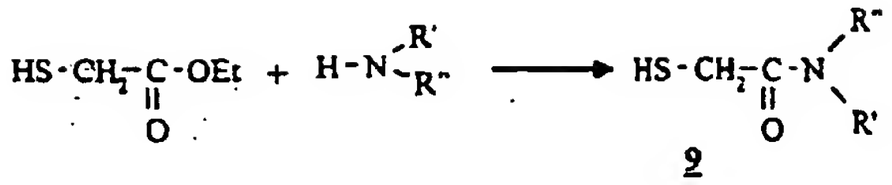

R1-Y-CH2-C≡C-CH2-S-CH2-CO2H
(I)
CDI or DCC
H-N
R'
R"
R1-Y-CH2-C≡C-CH2-S-CH2-C-N
O
(III)
Base +
HS-CH2-C-N
R1-Y-CH2[C≡C-CH2]m X
m=1,2,3
2, 4 or 7

Figure 7



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